

10/525,290

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L1 STRUCTURE UPLOADED

=> D L1

L1 HAS NO ANSWERS

L1 STR

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

Structure attributes must be viewed using STN Express query preparation.

=> S L1 FULL

FULL SEARCH INITIATED 14:45:09 FILE 'REGISTRY'

FULL SCREEN SEARCH COMPLETED - 76673 TO ITERATE

100.0% PROCESSED 76673 ITERATIONS

9 ANSWERS

SEARCH TIME: 00.00.05

L2 9 SEA SSS FUL L1

=> FILE CAPLUS

COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
172.55	172.76

FULL ESTIMATED COST

FILE 'CAPLUS' ENTERED AT 14:45:26 ON 30 MAR 2007

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FILE LAST UPDATED: 29 Mar 2007 (20070329/ED)

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=> S L2

L3 3 L2

=> D L3 IBIB ABS HITSTR 1-3

L3 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2005:158500 CAPLUS

DOCUMENT NUMBER: 142:261295

TITLE: Preparation of aryl carbamate oligomers for hydrolyzable prodrugs and prodrugs comprising same

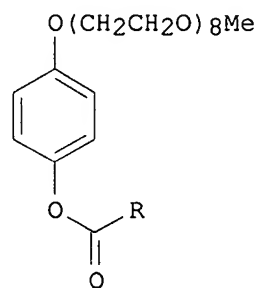
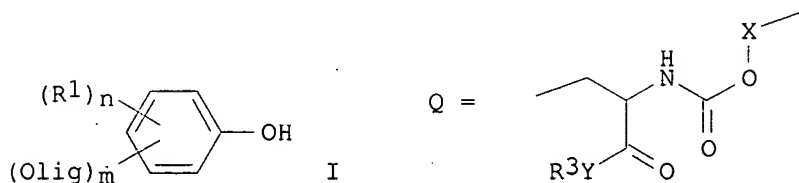
INVENTOR(S): Ekwuribe, Nnochiri N.; Odenbaugh, Amy L.

PATENT ASSIGNEE(S): Nobex Corporation, USA

SOURCE: PCT Int. Appl., 59 pp.

DOCUMENT TYPE: CODEN: PIXXD2  
 LANGUAGE: Patent  
 FAMILY ACC. NUM. COUNT: English 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005016240	A2	20050224	WO 2004-US15004	20040506
WO 2005016240	A3	20060928		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004264818	A1	20050224	AU 2004-264818	20040506
CA 2534298	A1	20050224	CA 2004-2534298	20040506
EP 1651163	A2	20060503	EP 2004-752108	20040506
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
US 2006167234	A1	20060727	US 2005-525290	20050718
PRIORITY APPLN. INFO.:			US 2003-491751P	P 20030801
			WO 2004-US15004	W 20040506
OTHER SOURCE(S):		CASREACT 142:261295; MARPAT 142:261295		
GI				



II

AB The present invention provides a compound having a formula: I [R1 = alkyl, -CH2(OC2H4)OMe, and (OC2H4)OCH3; n = 0-4; Olig = L-O-PAG-(R2)q; L = optional linker moiety CH2O, CH2OX, OX, CO, COX, NH, NHCO, XNHCO, NHCOX, CONH, CONHX, group Q; X = C1-6 alkyl, bond; Y = N, O, bond; R3 = C1-6

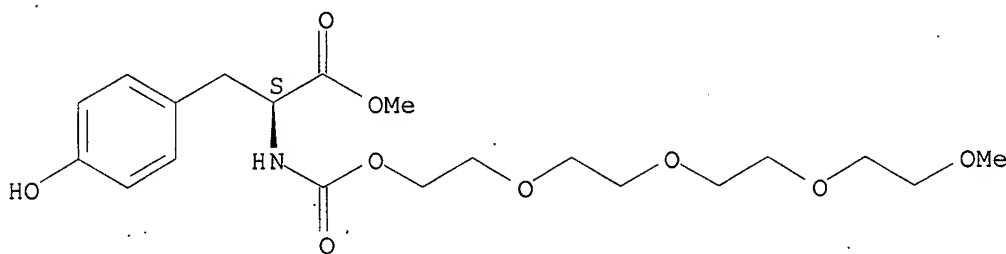
alkyl; PAG = linear or branched polyalkylene glycol moiety; R2 = C1-22 alkyl capping moiety if X is present or C2-22 alkyl capping moiety if X is not present; q = 1 to maximum number of branches on PAG; m = 1-5]. Thus, reaction of oligoethylene glycol mesylate  $\text{MeSO}_2\text{O}(\text{CH}_2\text{CH}_2\text{O})_4\text{Me}$  with 4-benzyloxyphenol, followed by hydrogenolysis of the benzyl group, activation with 4-nitrophenyl chloroformate, and reaction with leucine-enkephalin or human insulin gave prodrugs II (R = leucine enkephalin or insulin residue). Hydrolysis studies of the prepared prodrugs by carboxylesterase and in rat plasma are given.

IT 845910-83-ODP, tyrosine side chain conjugates with human insulin  
 RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (preparation of aryl carbamate oligomers for hydrolyzable prodrugs and prodrugs comprising same)

RN 845910-83-0 CAPLUS

CN 2,5,8,11,14-Pentaoxa-16-azaoctadecan-18-oic acid, 17-[(4-hydroxyphenyl)methyl]-15-oxo-, methyl ester, (17S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



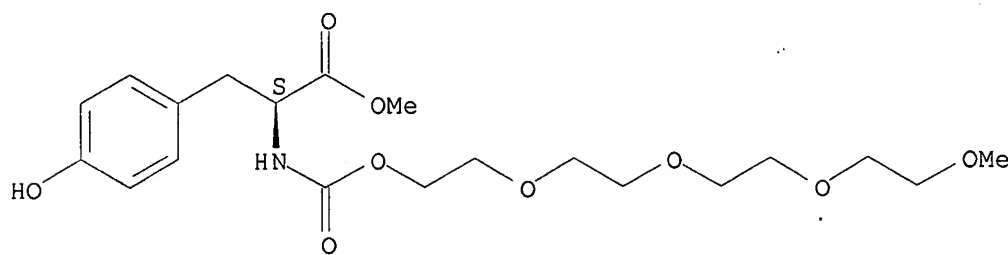
IT 845910-83-OP 845910-87-4P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of aryl carbamate oligomers for hydrolyzable prodrugs and prodrugs comprising same)

RN 845910-83-0 CAPLUS

CN 2,5,8,11,14-Pentaoxa-16-azaoctadecan-18-oic acid, 17-[(4-hydroxyphenyl)methyl]-15-oxo-, methyl ester, (17S)- (9CI) (CA INDEX NAME)

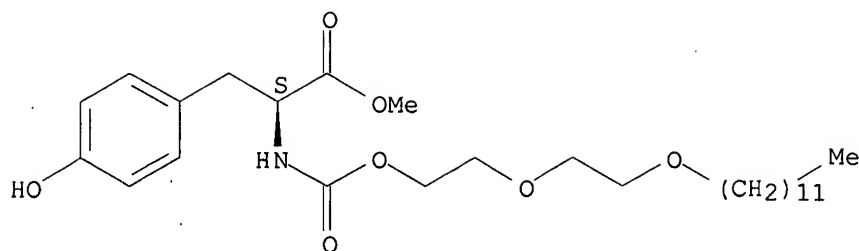
Absolute stereochemistry.



RN 845910-87-4 CAPLUS

CN 5,8,11-Trioxa-3-azatricosanoic acid, 2-[(4-hydroxyphenyl)methyl]-4-oxo-, methyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L3 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN  
 ACCESSION NUMBER: 1999:380315 CAPLUS  
 DOCUMENT NUMBER: 131:144830  
 TITLE: Synthesis and evaluation of the physicochemical properties of esterase-sensitive cyclic prodrugs of opioid peptides using an (acyloxy)alkoxy linker  
 AUTHOR(S): Bak, A.; Siahaan, T. J.; Gudmundsson, O. S.; Gangwar, S.; Friis, G. J.; Borchardt, R. T.  
 CORPORATE SOURCE: Department of Analytical and Pharmaceutical Chemistry, The Royal Danish School of Pharmacy, Copenhagen, DK-2100, Den.  
 SOURCE: Journal of Peptide Research (1999), 53(4), 393-402  
 CODEN: JPERFA; ISSN: 1397-002X  
 PUBLISHER: Munksgaard International Publishers Ltd.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 GI

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB The objective of this work was to synthesize the cyclic prodrugs I and II of [Leu5]-enkephalin (H-Tyr-Gly-Gly-Phe-Leu-OH) and DADLE (H-Tyr-D-Ala-Gly-Phe-D-Leu-OH), resp., using an (acyloxy)alkoxy linker. The cyclic prodrugs I and II were synthesized via a convergent method using the (acyloxy)alkoxy pro-moiety that connected the C- and N-terminus of the peptides. The cyclic prodrugs I and II exhibited Stokes-Einstein mol. radii similar to those of [Leu5]-enkephalin and DADLE; however, the cyclic prodrugs were shown to be significantly more lipophilic than the corresponding opioid peptides, as determined by partitioning expts. using immobilized artificial membrane (IAM) column chromatog. In addition, the cyclic prodrugs exhibit stable solution conformations, which reduce their hydrogen bonding potentials. Based on these physicochem. characteristics, the cyclic prodrugs I and II should have exhibited better transcellular flux across the Caco-2 cell monolayer than [Leu5]-enkephalin and DADLE, resp. However, the cyclic prodrugs I and II were shown in sep. studies to be substrates for P-glycoprotein, which significantly reduced their ability to permeate across Caco-2 cell monolayers. When P-glycoprotein was inhibited, the permeability characteristics of prodrugs I and II were consistent with their physicochem. properties.

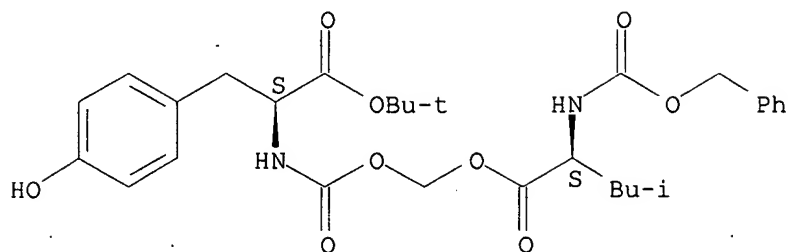
IT 236426-31-6P 236426-32-7P 236426-33-8P  
 236426-34-9P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (synthesis and peptide delivery activity of (acyloxy)alkoxy-containing cyclic prodrugs of opioid peptides)

RN 236426-31-6 CAPLUS

CN L-Tyrosine, N-[(hydroxymethoxy)carbonyl]-, 1,1-dimethylethyl ester,  $\alpha$ -ester with N-[(phenylmethoxy)carbonyl]-L-leucine (9CI) (CA INDEX NAME)

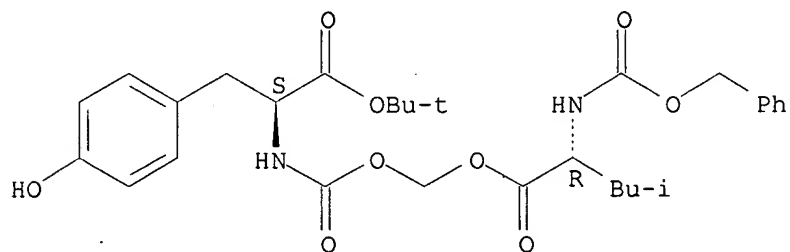
Absolute stereochemistry.



RN 236426-32-7 CAPLUS

CN L-Tyrosine, N-[(hydroxymethoxy)carbonyl]-, 1,1-dimethylethyl ester,  $\alpha$ -ester with N-[(phenylmethoxy)carbonyl]-D-leucine (9CI) (CA INDEX NAME)

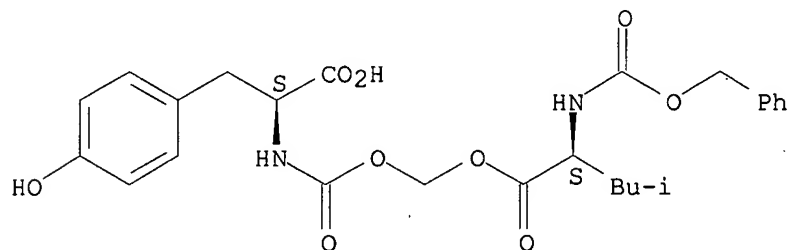
Absolute stereochemistry.



RN 236426-33-8 CAPLUS

CN L-Tyrosine, N-[(hydroxymethoxy)carbonyl]-,  $\alpha$ -ester with N-[(phenylmethoxy)carbonyl]-L-leucine (9CI) (CA INDEX NAME)

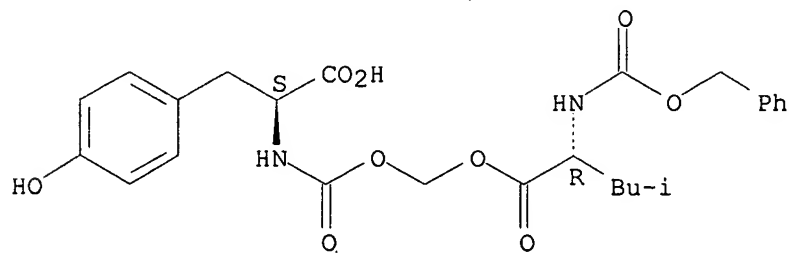
Absolute stereochemistry.



RN 236426-34-9 CAPLUS

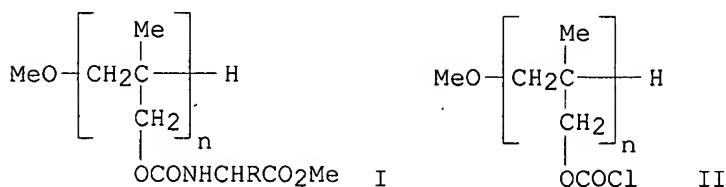
CN L-Tyrosine, N-[(hydroxymethoxy)carbonyl]-,  $\alpha$ -ester with N-[(phenylmethoxy)carbonyl]-D-leucine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



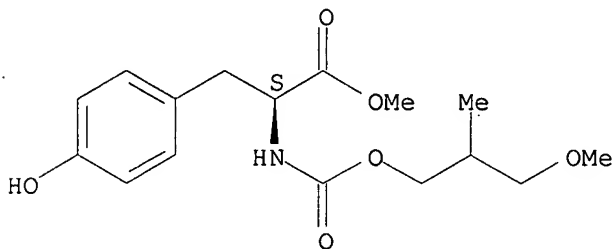
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN  
 ACCESSION NUMBER: 1986:207623 CAPLUS  
 DOCUMENT NUMBER: 104:207623  
 TITLE: Fixation of trifunctional amino acids on  
 oligomethacrylic supports. Tyrosine and glutamic acid  
 AUTHOR(S): Laguerre, A.; Rabadeux, J. C.; Gueniffey, H.; Bruneau,  
 C. M.  
 CORPORATE SOURCE: Fac. Sci., Univ. Maine, Le Mans, 72017, Fr.  
 SOURCE: European Polymer Journal (1985), 21(7), 619-22  
 CODEN: EUPJAG; ISSN: 0014-3057  
 DOCUMENT TYPE: Journal  
 LANGUAGE: French  
 GI

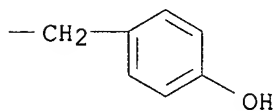
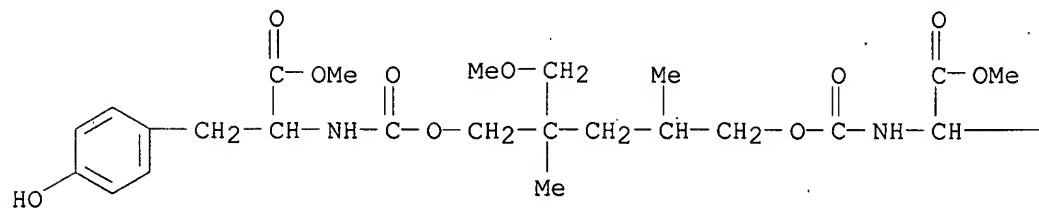


AB Tyrosine and glutamic acid were fixed by their NH<sub>2</sub> groups onto  
 oligomethacrylic supports through a urethane function. Polyfunctional  
 products able to act as precursors for networks are obtained. Thus,  
 fixation products I (R = CH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>OH-p, CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>Me; n = 1, 2, 3) were  
 prepared by treating chloroformates II with H<sub>2</sub>NCHRCO<sub>2</sub>Me.  
 IT 102039-89-4P 102039-90-7P 102059-99-4P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation of)  
 RN 102039-89-4 CAPLUS  
 CN L-Tyrosine, N-[(3-methoxy-2-methylpropoxy)carbonyl]-, methyl ester (9CI)  
 (CA INDEX NAME)

Absolute stereochemistry.

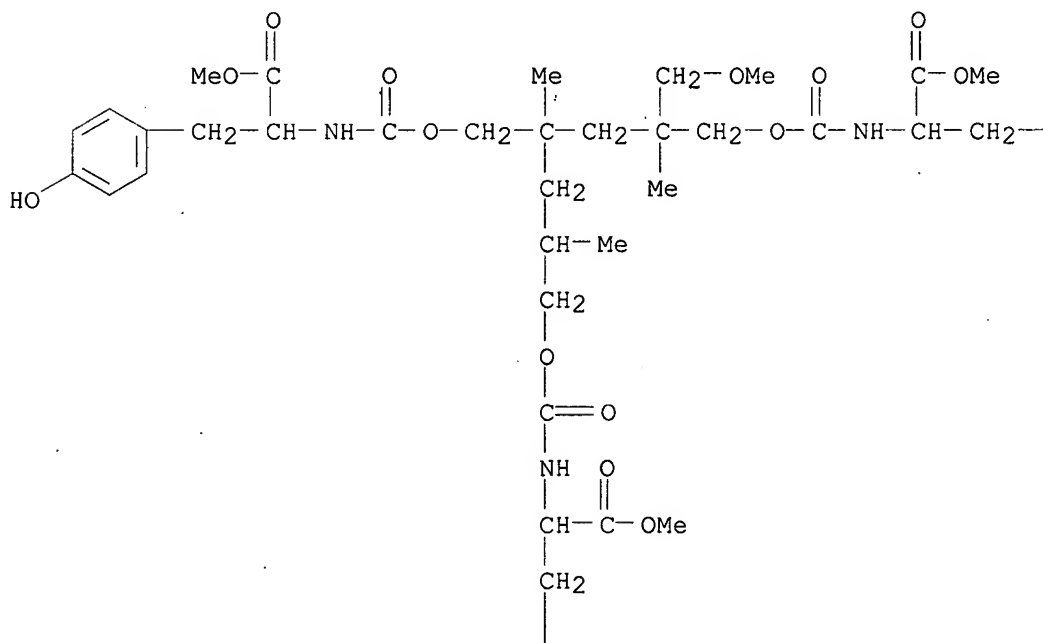


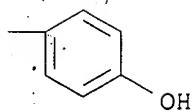
RN 102039-90-7 CAPLUS  
 CN 5,11-Dioxa-3,13-diazapentadecanedioic acid, 2,14-bis[(4-  
 hydroxyphenyl)methyl]-7-(methoxymethyl)-7,9-dimethyl-4,12-dioxo-, dimethyl  
 ester (9CI) (CA INDEX NAME)



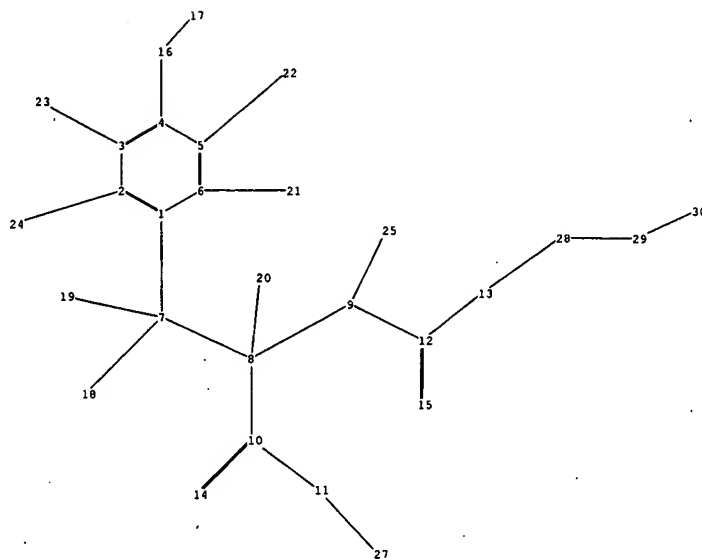
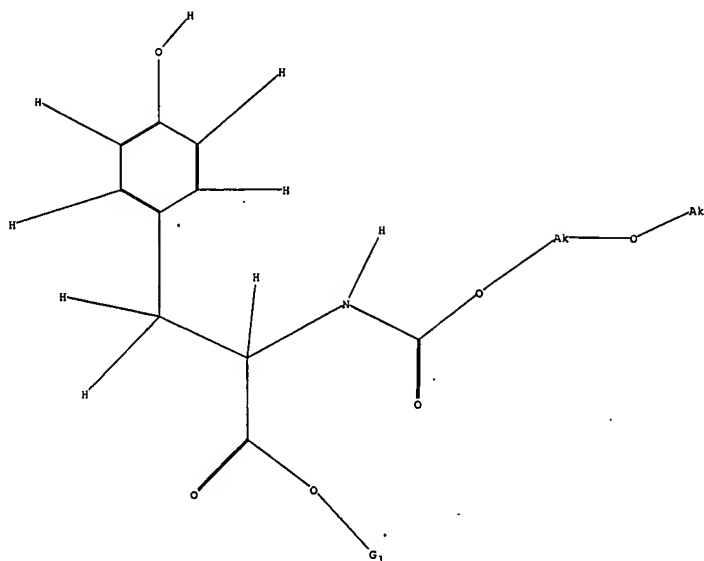
RN 102059-99-4 CAPLUS

CN 5,13-Dioxo-3,15-diazaheptadecanedioic acid, 2,16-bis[(4-hydroxyphenyl)methyl]-9-[[[1-[(4-hydroxyphenyl)methyl]-2-methoxy-2-oxoethyl]amino]carbonyloxy]methyl]-7-(methoxymethyl)-7,9,11-trimethyl-4,14-dioxo-, dimethyl ester (9CI) (CA INDEX NAME)









chain nodes :

7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 27  
28 29 30

ring nodes :

1 2 3 4 5 6

chain bonds :

1-7 2-24 3-23 4-16 5-22 6-21 7-8 7-18 7-19 8-9 8-10 8-20 9-12  
9-25 10-11 10-14 11-27 12-13 12-15 13-28 16-17 28-29 29-30

ring bonds :

1-2 1-6 2-3 3-4 4-5 5-6

exact/norm bonds :

4-16 8-9 9-12 10-11 10-14 11-27 12-13 12-15 13-28 28-29 29-30

exact bonds :

1-7 2-24 3-23 5-22 6-21 7-8 7-18 7-19 8-10 8-20 9-25 16-17

normalized bonds :

1-2 1-6 2-3 3-4 4-5 5-6

G1:H,Ak

Match level :

1:Atom	2:Atom	3:Atom	4:Atom	5:Atom	6:Atom	7:CLASS	8:CLASS	9:CLASS
10:CLASS	11:CLASS	12:CLASS	13:CLASS	14:CLASS	15:CLASS	16:CLASS		
17:CLASS	18:CLASS	19:CLASS	20:CLASS	21:CLASS	22:CLASS	23:CLASS		
24:CLASS	25:CLASS	27:CLASS	28:CLASS	29:CLASS	30:CLASS			